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Posttraumatic Stress Disorder: Emerging Concepts of Pharmacotherapy

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Abstract

Posttraumatic stress disorder (PTSD) can result from a traumatic experience that elicits emotions of fear, helpless or horror. Most individuals remain asymptomatic or symptoms quickly resolve, but in a minority intrusive imagery and nightmares, emotional numbing and avoidance, and hyperarousal persist for decades. PTSD is associated with psychiatric and medical co-morbidities, increased risk for suicide, and with poor social and occupational functioning. Psychotherapy and pharmacotherapy are common treatments. Whereas, research supports the efficacy of the cognitive behavioral psychotherapies, there is insufficient evidence to unequivocally support the efficacy of any specific pharmacotherapy. Proven effective pharmacologic agents are sorely needed to treat core and targeted PTSD symptoms, and for prevention. This review describes current and emerging pharmacotherapies that advance these goals.

1.0 Background

Vignettes of behavior in literature from Homer's *Iliad* to the writings of 19th century physicians, Charcot and Janet, provide credible descriptions of the impact of traumatic stress on the human mind [1-3]. However, the behavior described was not acknowledged by the medical community as a distinct clinical entity until 1980, when behavioral changes that follow life-threatening events were first codified into the diagnostic criteria for posttraumatic stress disorder (PTSD) and were included in the Diagnostic and Statistical Manual of Mental Disorders Version III (DSM-III). The original diagnostic criteria were revised in 1987 (DSM-III-R) and 1994 (DSM-IV), but remained unchanged during criteria review in 2000 (DSM-IV-TR) [4]. Posttraumatic stress disorder is unique among the mental health disorders in that like infectious disease that requires exposure to a pathogenic vector as well as a vulnerable host to precipitate illness, an external stimulus, i.e. a life-threatening or traumatic event is thought to precede and precipitate the emergence of PTSD symptoms in susceptible individuals unlucky enough to be so exposed. This external stimulus has been incorporated into the DSM diagnostic criteria as Criterion A, defined as having experienced both a traumatic stress ("experienced or witnessed actual or threatened death, injury or threat to the physical integrity of self or others") and having reacted

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with “intense fear, helplessness or horror”. In societies where rates of exposure have been measured, the lifetime prevalence of experiencing a traumatic event is reported to be between 17% and 89% [5-13]. The DSM-IV definition does not recognize inherent pathogenic differences in the “vector”, e.g. differences in type of trauma exposure or in repeated versus single exposure. However, there is some evidence that duration and intensity of trauma exposure, and the risk for PTSD as a result of that exposure follow a dose-response relationship, and that some types of events are more “pathogenic” than others [8, 9, 14-18].

The behavioral manifestations that result from exposure to a Category A event in vulnerable individuals constitute additional diagnostic criteria for PTSD including intrusive recollections of the traumatic event (Criteria B), avoidance and emotional numbing (Criteria C), and hyperarousal, e.g. irritability, difficulty sleeping and increased startle reactivity (Criteria D). These PTSD symptoms must be present for at least one month (Criteria E) and must cause distress and impairment in various areas of functioning (Criteria F) [4]. As defined in DSM-IV, PTSD symptom duration between one and three months is considered to be acute PTSD and duration of three months or longer is considered to be chronic PTSD. The disorder can also be delayed in onset, defined as commencement of symptoms occurring at least six months after trauma exposure. The common lexicon provided by DSM diagnostic criteria has formed a basis for the design and execution of the currently available epidemiological, neurobiological and treatment research on PTSD.

A recent assessment of symptoms following comparable traumatic events, terrorist bombings in Oklahoma City, United States and in Nairobi, Kenya, demonstrated remarkable cross-cultural similarity in PTSD symptom expression [19, 20]. The incidence of PTSD by gender across sites was also similar, with females showing higher rates of illness, a finding common to virtually all epidemiological studies of PTSD. Large-scale epidemiological studies of lifetime and 12-month prevalence of PTSD have been completed in Europe, Australia and North America, with data showing lifetime rates of PTSD ranging from 1.9% (Europe) to 6.8% (North America) [5, 10, 18, 21]. To date there are no large scale epidemiological studies in areas of the world recently impacted by war and massive natural disasters, e.g. sections of the Middle East, Africa and Asia, where rates of trauma exposure and lifetime prevalence of PTSD may well exceed those found in Europe, Australia and the Americas [22, 23].

In common with infectious vectors, data show that PTSD “vectors”, i.e. rates and types of DSM-IV Category A events, differ by locale and by demographic factors, such as age and gender; this variation is thought to account in part for discrepancies in PTSD lifetime and 12-month prevalence found in the epidemiologic literature [8, 9, 18]. There are ongoing attempts to define the relationship between type and number of Category A trauma event(s) and PTSD outcome. Studies have shown that many individuals who have experienced at least one trauma event have experienced multiple events, that adults with a PTSD diagnosis report elevated rates of prior trauma events, and that some types of events appear to be more “pathogenic”, i.e, more highly associated with subsequent PTSD than others [9, 17, 18, 24-28].

However, a recent longitudinal epidemiological study highlights the complexity of the Category A – PTSD outcome relationship by showing that PTSD susceptibility impacts trauma exposure risk and by highlighting the importance of “host” vulnerability/resilience factors for conditional risk for PTSD over time [29]. In this study of young adults the original cohort was subsequently interviewed over a 10 year timeframe. The respondents who had developed PTSD from a prior, index event had the highest likelihood of exposure to further traumatic events during the 10 year follow-up period, and respondents who had experienced a prior trauma but did not have PTSD had an intermediate likelihood of trauma exposure when compared to the reference group, subjects with no prior trauma exposure [29]. Also, a preexisting diagnosis of major depression was associated with an elevated rate of trauma exposure during the 10-year

follow-up period, thus pointing to various "host" characteristics that impact exposure risk and possible PTSD outcome [29]. Even after controlling for relevant confounding factors, the conditional risk of PTSD during the 10 year follow-up period was significantly higher among trauma-exposed individuals who had experienced prior PTSD, relative to those who had experienced no prior trauma. In contrast, the conditional risk of PTSD during the follow-up period of individuals who had experienced prior trauma but not PTSD was not significantly elevated [29]. These data are consistent with studies that show the genetic contribution to PTSD, which is about 20-30%, to be complex; that the likelihood of exposure to traumatic events is not random, but is influenced by both individual and familial risk factors, some of which increase vulnerability to the exposure of life-threat events, and others that increase PTSD risk in individuals exposed [See also Baker et al. [30] for review] [16, 31-35].

Longitudinal studies have grown in number since the late 1980s, and although they continue to be only a fraction (between 2.5% and 3.1%) of all PTSD research, they have contributed unique information about the natural history of the disorder [36]. Specifically these studies have shown that there are a number of post-trauma symptom trajectories and that in fact, consistent with other data showing considerable inter-individual variability in vulnerability/resilience factors, most individuals exposed to a trauma event do not succumb to chronic PTSD. These studies show that post-trauma PTSD symptoms are common, that most trauma-exposed individuals who initially have symptoms show a time-dependent post-event progressive decline in PTSD symptoms, and that individuals who do go on to develop PTSD have a distinctly different symptom course than those who recover [36]37. Longitudinal studies replicate findings from cross sectional and genetic research that show that individual traits such as intelligence, gender, and environmental factors such as childhood adversity are predictors of the vulnerability/resilience profile for chronic PTSD following trauma exposure [36, 38-40].

In individuals who meet criteria for the core PTSD symptoms, co-occurring psychiatric disorders are more common than not, with the vast majority of large epidemiological studies reporting lifetime rates of co-morbid psychiatric disorders at 80% or greater [5, 7, 11]. The most common co-morbidities are major depression, other anxiety disorders, and substance use disorders. But other psychiatric disorders, e. g. bipolar disorder and psychoses are also observed at higher rates in individuals with PTSD than without. These co-morbid disorders must be assessed and accounted for in the choice of psychopharmacologic interventions [41-45]. Given that prior research has largely been cross-sectional, it is as yet unclear whether co-morbidities that accompany PTSD are more commonly triggered along with PTSD symptoms after exposure to a trauma event, emerge gradually after PTSD development, or are pre-existing conditions that constitute heritable risk factors for vulnerability. A recent longitudinal study that attempts to address this question found that virtually all individuals diagnosed with PTSD at age 26 had prior mental health diagnoses (93% lifetime) [46]. Individuals assessed at age 26 who had not yet developed PTSD were then followed prospectively over a four year timeframe between ages 26 and 32; 96% of members of that cohort who developed PTSD had a prior diagnosed mental disorder, 77% before the age of 15 [46]. However since PTSD had not been assessed and diagnosed in this cohort along with other mental health disorders during the timeframe from birth to age 26, conclusions about whether trauma exposure, and PTSD were primary, or secondary to the co-morbidities was not ascertainable within the research design employed [46].

PTSD is associated with high levels of impairment across social and occupational domains [41, 47]. The work loss index and role disability of individuals with PTSD is high, rivaling that of neurological disorders and exceeding that of diabetics [48]. Annual productively loss from PTSD in the United States is estimated to be over three billion US dollars [49]. In contrast to other anxiety disorders studied, PTSD is independently and significantly associated with both

suicidal ideation and suicide attempts after controlling for covariates such as co-morbidity [50, 51].

Studies in which the prevalence of partial, or sub-threshold PTSD was examined found it to be substantial. A large Canadian epidemiological study assessing for current PTSD found the incidence to be 5.0% (women) and 1.7% (men), but the incidence of partial PTSD to be even higher at 5.7% and 2.2% for women and men respectively [52]. Individuals with sub-threshold PTSD showed similar levels of social and occupational impairment as those meeting full criteria [52, 53]. Functional impairment, rates of co-morbid disorders, and rates of suicidal ideation were shown to increase linearly with increasing number of PTSD symptoms, and individuals with sub-threshold PTSD had increased suicidal ideation even after controlling for the presence of co-morbid major depressive disorder [53].

Current theories or models that provide a framework for conceptualizing PTSD are: 1) A fear conditioning model, which involves an associative link between the aversive event, a psychophysiological response and memory encoding, and the subsequent involuntary activation of the memory in the form of PTSD symptoms [54], 2) A biological theory based on pre-clinical and neuroendocrine studies that show a persistent central hyperarousal, abnormalities in glucocorticoid feedback and inadequate or ineffective stress-system (e.g. serotonin, neuropeptide Y) modulation [see Charney [55] for review] and 3) a psycho-neuroanatomical model, that suggests traumatic recollections are initially encoded as unelaborated emotional memories and later have to be transformed into autobiographical or episodic memories through encoding [56]. None of these models provides an etiological explanation for PTSD, but they represent the state-of-the-art currently available to inform rationale for pharmaceutical treatments and development of novel interventions [55, 57]. In addition to the above explanatory models, there is an emerging understanding that there is population variability in trauma response as a result of “host” vulnerability/resilience factors. Moreover, there may be critical post-trauma timeframes for the resolution of symptoms, and that if the biological dynamics are fully understood, these timeframes may provide opportunities for interventions that might abort emergence of chronic symptoms. Toward this end, intervention research has been directed at psychotherapeutic and pharmaceutical strategies such as prophylaxis, i.e. prevention and early intervention, as well as at treatments for chronic PTSD [58]. Therefore in this manuscript, pharmacologic initiatives for development of drugs for prophylaxis, in the form of prevention and early intervention will be discussed along with the scientific rationale and initiatives for development of interventions for treatment of chronic PTSD.

2.0 Medical Need

In comparison to pharmaceutical development for DSM diagnoses such as depression and psychosis, that were formally codified earlier in the 20th century, the number and breadth of PTSD pharmaceutical treatment studies has been relatively few, and the need for expanded treatment options is especially great. Serotonin re-uptake inhibitors (SSRIs), the most commonly prescribed medications for chronic PTSD are not effective in about 40% of patients, and even in partial responders, additional medications such as sedating antidepressants or sedative/hypnotics are frequently needed to target refractory symptoms, such as sleep disturbance, nightmares, or panic/anxiety symptoms. Moreover, despite being relatively safe, the use of SSRIs can be limited by potential side effects; especially sexual or gastrointestinal side effects or less commonly fatigue, akasthisia or other adverse experiences.

There is a clear need for a broader array of effective medications for chronic PTSD as a whole, as well as for effective medications to target refractory symptoms, such as sleep or panic anxiety. Additionally, development of novel psychotherapeutic and pharmaceutical

interventions for early intervention would also be beneficial, as would adjunctive medications that might improve upon the efficacy of currently accepted cognitive behavioral interventions for chronic PTSD, such as cognitive processing therapy (CPT) or prolonged exposure therapy (PE). Unfortunately, drug development in PTSD suffers from a drawback common to that of other mental disorders; whereas there have been spectacular advances in our understanding of the brain and its function over the past half century, the causal neurobiology of these disorders, including PTSD is yet to be elucidated [55, 57].

3.0 Existing Treatment

Within the past three years a number of extensive and systematic reviews of the efficacy of pharmacotherapy and other PTSD treatments have been published including manuscripts from The Institute of Medicine (IOM), the National Institute of England (NICE), and the Australian Center for Public Health), among others [59-62]. The entities that reviewed currently used psychotherapies agree that various cognitive behavioral treatments, especially PE and CPT, have proven efficacy in treatment of PTSD. However, adequately powered and well-designed PTSD pharmaceutical studies are few; only 37 were deemed acceptable for review by the IOM and the Cochrane Review. And overall, there is less concordance about the proven efficacy of pharmacotherapy than of psychotherapy; IOM and NICE argue that there is insufficient evidence to show proven efficacy of any drug or drug class, whereas the Cochrane Reviews and some others endorse the use of pharmacotherapy as a first line treatment [59-62]. However, the Cochrane Review concludes that there is no clear evidence to show that any particular class of medication is more effective or better tolerated than any other, while noting also that the greatest number of trials, as well as the largest, showing efficacy to date have been with SSRIs [60-62].

In actual practice, medications are commonly used in the treatment of PTSD [63, 64]. A review of US Department of Veterans Affairs pharmacy records in fiscal year 2004 revealed that most veterans diagnosed with PTSD received psychotropic medication (80%); and among these, 89% were prescribed antidepressants, 61% anxiolytics or sedative-hypnotics, and 34% antipsychotics [63]. Pharmacotherapy is nearly as common in the civilian sector. Data from the Marketscan database, a database that compiles claims from US private insurers show that of adult mental health care users with PTSD, sixty percent received a psychotropic medication. Among those who received medications, 74.3 % received antidepressants, 73.7% received anxiolytics or sedative hypnotics, and 21% received antipsychotics. Having a co-morbid diagnosis was the most robust predictor of medication use for both the veteran and civilian groups, and whereas disease-specific use for both PTSD and co-morbid disorders was common, substantial use seemed to be unrelated to diagnosis, thus was likely to be targeting specific symptoms (e.g. insomnia, anxiety, nightmares, intrusive imagery), rather than diagnosed illness [63, 64]. The overall cost of the illness and treatment interventions is difficult to determine, however. Although a large number of mental health economic studies have been conducted, none have focused specifically on interventions for PTSD [65, 66].

Here, we define *therapeutic* treatments as those that reduce current symptoms, either as a whole, or in a targeted manner, e.g. treatment of insomnia, or nightmares. To date pharmacotherapy has predominantly targeted chronic PTSD; only recently have prophylactic or adjunctive treatments been investigated. Of the published pharmaceutical trials, only 37 randomized clinical controlled trials (RCTs), all of which target chronic PTSD symptoms, were deemed of sufficient quality for review by the IOM and Cochrane Reviews [61, 62]. Drug classes reviewed include antidepressants, e.g. SSRIs, monoamine oxidase inhibitors, tricyclics, as well as alpha-adrenergic blockers, anticonvulsants, benzodiazepines, novel antipsychotics, and others such as d-cycloserine and inositol [61, 62].

Most of the compounds in the RCTs reviewed are thought to act by dampening the generalized arousal and anxiety experienced by PTSD patients [67]. Below, we review some of these therapeutic classes. Later in the manuscript, under scientific rationale we also review some novel agents under investigation in pre-clinical or early clinical trials that may ultimately prove valuable as pharmacologic agents if brought to market.

3.1 Serotonin reuptake inhibitors

The putative mechanism of action of SSRIs is the blockade of the reuptake of serotonin in certain synapses in the brain. As with most currently used pharmaceutical agents, investigation of their efficacy in PTSD was initiated after studies showed their efficacy in depression and other anxiety disorders. Data from studies of two SSRIs, sertraline and paroxetine have been submitted to the Federal Drug Administration (FDA), and the data were deemed adequate to gain indication for use of these SSRIs in treatment of chronic PTSD [68-71]. In practice, SSRIs are typically the first line treatment, and the various SSRIs, e.g. sertraline, paroxetine, citalopram, fluoxetine, escitalopram are often prescribed interchangeably for treatment of chronic PTSD based on factors, such as cost and side effect profile. Some PTSD symptoms, such as irritability appear to respond better to SSRIs than others, such as sleep disturbance. Often sexual side effects are limiting, especially in young men. SSRIs have not shown uniform efficacy across studies; symptom improvement has varied across different populations and/or trauma types, e.g. by gender and between civilian and veteran cohorts [62,72]. In a recently published study in which an SSRI was prescribed as an adjunct to enhance response to psychotherapy, it showed no added treatment benefit [73].

3.2 Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOI) act by preventing the breakdown of monoamine neurotransmitters and thereby increase their availability. There are four RCTs examining the effects of two MAOIs, in the treatment of PTSD, phenelzine, a non-selective MAOI and brofaromine, a selective MAOI-A inhibitor [6, 74-76]. The studies, which showed mixed efficacy, were small and of variable design quality. Thus interpretability of their efficacy is difficult. In practice, MAOIs are rarely prescribed for use in PTSD because of fears of the side effect profile of these drugs. Selegiline, the reversible and relatively selective MAOI-B inhibitor that can be delivered via a transdermal patch, would potentially circumvent some of the dietary side effect concerns. A meta-analysis of clinical trials of seleginine in dysthymia and major depression failed to show efficacy despite positive attributes, such as neuroprotective effects. Its efficacy has not been studied in PTSD.

3.3 Novel Antipsychotics

Clinically, antipsychotic medications are frequently used as adjunct treatment in civilian and veterans with PTSD, especially in patients with mental health co-morbidities or who have refractory symptoms, e.g. sleep disturbance [63, 64]. Serious adverse effects, e.g. tardive dyskinesias, weight gain and altered glucose tolerance are potential limiting factors, especially since chronic PTSD may be associated with metabolic syndrome and risk for cardiac disease [77-79]. There have been eight published RCTs of two different antipsychotics, risperidone and olanzepine, in PTSD [80-87]. The studies were small, of variable design quality and have generally focused on special features of PTSD, such as refractoriness to treatment or associated psychotic features [81, 83, 85]. In six trials of risperidone it was used as an augmentation to other medications, rather than as a primary treatment. All except one of these studies showed risperidone to be effective used in this way [80-84, 87]. Based on these findings, a large, multi-site trial of risperidone is now underway in the United States in veterans to determine its effectiveness as an adjunct treatment in individuals with treatment resistant, chronic PTSD.

3.4 Anticonvulsants

Anticonvulsants are used in PTSD to treat co-morbid disorders, such as bipolar affective disorder (BAD), or to target symptoms such as impulsive anger. BAD is observed at higher rates in individuals with PTSD; the combination of disorders is especially destabilizing; and unfortunately the co-morbidity is easy to miss clinically. Anticonvulsants, e.g. valproic acid, are generally effective in restoring emotional stability and improving social functioning when prescribed to patients with PTSD and BAD. Unfortunately there are no RCTs of the use of anticonvulsants in co-morbid PTSD-BAD. A study of valproate in the treatment of impulsive aggression that included PTSD subjects had insufficient numbers for analysis of efficacy in treating core PTSD symptoms [88]. More recently, a study of valproate in the treatment of core PTSD symptoms showed no efficacy [89]. RCTs of three other anticonvulsants, tiagabine, topiramate, and lamotrigine have been completed with variable results, negative for tiagabine and topiramate and positive for lamotrigine, although the lamotrigine study was too small (n = 15) to show statistical significance or to estimate an effect size [89-92].

3.5 Alpha adrenergic blocking agents

There are two small RCTs and a cross-over study of prazosin, an alpha1-adrenergic blocker showing suggested efficacy for nightmares and sleep disturbance in PTSD [93-95]. The goal of these studies was not evaluation of overall PTSD symptoms, but evaluation of targeted symptoms, which showed good outcomes, e.g. a reduction in nightmares, and polysomnographic evidence of an increase in total sleep time, REM sleep time, and mean REM period duration, without sedative-like effects. High doses of prazosin are sometimes required; limiting side effects include orthostatic hypotension and sometimes headache. Based on findings from these smaller studies, a large, multi-site trial of prazosin is now underway in United States veterans. An RCT of guanfacine, an alpha- blocking agent failed to show efficacy for global or targeted symptoms of adults with PTSD [96].

3.6 Benzodiazepines

Clinically, benzodiazepines are sometimes used to target panic/anxiety symptoms, or to target sleep difficulties. Given the high co-morbidity of PTSD with substance abuse disorders, a complete assessment of co-morbidities and a consideration of the addictive potential of the benzodiazepines being prescribed are necessary. There are few RCTs of the use of this class of drugs in PTSD; one a clinical trial of alprazolam in treatment of chronic PTSD, and the other for use of the benzodiazepines, alprazolam or clonezepam, in the prophylaxis of PTSD [97, 98].

3.7 Other antidepressants

When SSRIs fail to alleviate PTSD symptoms or when depressive symptoms accompanying PTSD are unresponsive, the common practice is to prescribe other antidepressants, including dual serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, or atypical antidepressants, e.g. buproprion. These antidepressants are variably effective, and are limited by side effects common to their class. Unfortunately RCTs of these antidepressants in the treatment of PTSD are few; there are three trials of tricyclics, two of venlafaxine, one of mirtazepine and one of nefazodone [62]. All RCTs show modest improvements in PTSD symptoms, but all are small or have limiting design and/or data handling issues that limit their interpretability. For example, in two studies of venlafaxine that show some improvement in symptoms, dropout rates exceeded 30% [99, 100]

3.8 Miscellaneous

Small RCTs of d-cycloserine and inositol to treat global symptoms of chronic PTSD showed no efficacy. There are a number of ongoing trials of the use of d-cycloserine as an adjunct treatment for PE. See scientific rationale for greater detail.

4.0 Current Research Goals

Research into novel PTSD treatment strategies have been directed at a number of different goals. These include: 1) Mitigation of global reduction of symptoms and general anxiety levels in individuals with chronic PTSD, predicated upon normalizing putative underlying pathological processes, 2) Mitigation of targeted symptoms, e.g. sleep, nightmares, irritability, predicated upon modifying biological processes driving those symptoms, 3) Use of medication as an augmentation strategy to various types of psychotherapy, e.g. as an additional treatment to enhance reduction in global symptoms [101], or as an adjunct to improve the learning expected to take place in exposure therapy [102].

Adjunctive treatments are defined in this manuscript as synergistic treatments that aid efficacy and response time to other pharmacological treatments or psychological therapies, in particular exposure therapy, such as PE designed to facilitate the extinction of fear memory [103]. Rothbaum and Davis describe PTSD as a disorder characterized by a "failure of fear extinction after trauma" [104]. In animals and humans, a conditioned fear association occurs when a conditioned stimulus (CS) and an aversive unconditioned stimulus (US) are presented in close temporal proximity. Thus the subject learns that the CS "predicts" the occurrence of the US. In the case of PTSD, environmental cues during trauma are associated with the pain and fear of the traumatic event, and these cues continue to evoke strong fear reactions long after the initial trauma has receded. In the laboratory this phenomenon is modeled in humans and animals by pairing a tone or light with noxious stimuli such as an electrical shock. Once the association between the CS and US has been learned, the presentation of the CS alone will invoke a conditioned fear response (e.g. autonomic activation, exaggerated startle response, avoidance behavior). The phenomenon of fear extinction occurs when the learned CS is then presented without the occurrence of the US, hence the subject learns that the CS no longer predicts the presence of the US and subsequent fear responses to the CS are inhibited or "extinguished". It is this phenomenon that is hypothesized to be disrupted in PTSD patients, which continue to show pronounced signs of anxiety, avoidance, and arousal in response to trauma reminders.

Research on the biological basis of fear extinction has exploded [see Quirk and Mueller [105] for review]; however, in this manuscript we will focus on systemic studies of drugs that facilitate extinction learning.

As noted in the background section, there is an emerging awareness that pharmacologic interventions given in the immediate or acute post-trauma timeframe may be effective as a *prophylaxis*, in preventing symptom consolidation and aborting the development of chronic PTSD. Conceptually there are two intervals: the immediate (0-48 hour) and the acute (within a few weeks post trauma) periods when prophylactic interventions are indicated [58]. However, ethical issues emerge in the use of both psycho- and pharmaco-therapy as prevention/early intervention strategies. Given our current inability to easily and accurately predict symptom trajectory, the specific benefit/risk ratio for any specific treatment must be carefully considered. Since prevention and early intervention is hampered by incomplete knowledge about host factors that predict trajectories of adaptation to various traumas and the biological underpinnings of that adaptation, longitudinal studies of these phenomena are sorely needed [58]. Moreover, the ethical issues of memory blockade (especially when legal proceedings will follow the traumatic event) have also produced a flurry of debate [See Henry et al. [106] and letter responses]. Some drugs that are being evaluated as prophylactic treatments have proven amnesic properties (e.g. ketamine), while others have been used in the clinic for many years with low cognitive side effects (e.g. propranolol).

Presently, the prime rationales for intervention in the acute aftermath of trauma have been to either dampen arousal and/or enhance biological resilience. Many stress systems (e.g.

norepinephrine, CRF, corticosterone) have been shown in preclinical studies to strengthen fear memories; hence have been considered targets for inhibitors to attenuate memory strength without cognitive impairment. Drugs given for early intervention would theoretically be effective if they aid in reducing fear memory consolidation and/or attenuate strong coupling of the memory with intense physiological responses [107]. Certainly there are individual differences in how people respond and adapt to traumatic stress, and understanding these mechanisms may help us develop novel treatments. Toward that end, recent work has focused on potential epigenetic contributors to the biological plasticity underlying fear learning and extinction [32, 108, 109]. Based on the pre-clinical work demonstrating that chromatin-modifying enzymes may play a role in fear memories, Nestler and his colleagues postulate that post-trauma resilient behavior represents a distinct, active neurobiological process [32, 110]. If these epigenetic mechanisms prove correct, they may offer viable targets for drug development. Post-trauma resilient behavior may also depend on modulatory neurochemicals and neuropeptides, e.g. serotonin, neuropeptide Y and others. For example, there is some support that mutations in the human serotonin transporter gene (SLC6A4), located in the 5′ region (5 HTTLPR) are associated with increased risk for depression and anxiety disorders [111-116], anxiety traits [117], differential acquisition of conditioned fear and increased amygdala excitability [118, 119], and that they may be associated with measures of resilience [120] and vulnerability to PTSD [121, 122].

5.0 Scientific Rationale

In contrast to the section “existing treatment”, and the table in the section “competitive environment”, we focus this section is on scientific rationale in support of novel treatment targets currently limited to preclinical testing and/or early proof of principle clinical trials.

5.1 Steroids/Glucocorticoids

Glucocorticoids serve as modulators of the corticotropin releasing factor (CRF) signal, positively increasing CRF in limbic circuits in response to environmental stress [123, 124]. Although there is a large literature on glucocorticoids and the HPA axis in PTSD, the literature remains controversial and conflicted. There is some evidence for abnormalities including peripheral hypocortisolemia and enhanced hypothalamic-pituitary-adrenal (HPA) axis negative feedback but findings are not consistent, consequently the authors of a recent review suggest the need for cerebrospinal fluid (CSF) studies [125-127]. Baker et al. have shown normal plasma, but elevated cerebrospinal fluid (CSF) cortisol concentrations in chronic PTSD, as well as a positive correlation between CSF CRF and CSF cortisol concentrations [128]. These findings have yet to be replicated. However, based on preclinical models and upon clinical hypotheses, both glucocorticoid agonists and antagonists have been proposed.

5.1.1 Agonists—Pre-clinical models suggest that ability to mount a glucocorticoid response to stress may predict resilience to PTSD [129]. Data from some human studies show plasma cortisol levels to be negatively correlated with PTSD symptom severity [130]. Hypothesized mechanisms underlying possible glucocorticoid facilitation of resilience are via either facilitation of extinction or impairment of fear memory retrieval, given that glucocorticoid receptor agonists increase extinction and impair fear memory recall in rodent models of fear learning [131, 132]. Moreover surgical patients given preoperative hydrocortisone showed a reduction in PTSD symptoms post operatively [133], providing clinical support to the hypothesis that cortisol release during trauma may be important for preventing chronic PTSD. A very small double-blind placebo controlled cross-over study (n=3) also showed some promising effects of hydrocortisone in reducing trauma memories [134], which may be related to its effects in blocking memory recall or fear extinction [135]. Hydrocortisone treatment is currently under

examination in at least 3 clinical trials as adjunctive treatment with extinction based therapies (clinicaltrials.gov).

5.1.2 Glucocorticoid Antagonists—In rodents glucocorticoid antagonists have been shown to disrupt fear memory consolidation when given immediately after training, hence in theory they have prophylactic utility [136, 137] when given immediately after trauma. We must be cautious however as glucocorticoids have been shown to facilitate extinction in pre-clinical studies as indicated above [131], thus the post trauma timeframe in which these treatments are being administered, immediately after trauma or during the extinction phase of trauma, may be crucial [135]. Based on the administration timeframe, they may be beneficial or harmful. Small studies (n = 30) of psychotic depression and bipolar disorder thus far using a non-selective glucocorticoid receptor antagonist Mifepristone (RU-486), otherwise known as the morning after pill, are reported to show promise in reducing cognitive disruption and psychosis [138, 139]. There are currently 4 listed clinical trials for mifepristone treatment in PTSD, with one recently completed. Outstanding issues in regard to use of glucocorticoid antagonists for PTSD remain. These include: 1) Their site of action, i.e. the pituitary versus the brain, has not been clarified. 2) The findings from these small depression studies are yet to be replicated in large, or multi-site trials. 3) Lastly, there are no published reports of the efficacy of glucocorticoid antagonists in PTSD.

5.2.0 Glutamate signaling

5.2.1 Ionotropic glutamate receptor ligands—Preclinical studies have demonstrated that glutamate transmission in the amygdala is necessary for fear extinction (FPS). [For review see Meyers and Davis [140]]. Much research has centered around the finding that d-cycloserine (DCS), a partial NMDA (N-methyl-D-aspartic acid) receptor agonist acting on the glycine modulator site, significantly enhances extinction when given during or immediately after extinction training [141], with a recent meta-analysis across animal and human literature confirming the DCS effects in enhancing extinction across multiple studies [142]. Some caution must be taken, as one preclinical study indicates that DCS may facilitate reconsolidation when the subject is given a limited number of exposures [121]. Thus more research is required in understanding the critical factors (number of sessions, dose, time of treatment, most responsive population) that impact the DCS efficacy as adjunctive therapy [143-145]. DCS has shown some efficacy as an adjunctive treatment in certain anxiety disorders [For review see Norberg et al. [142]], but it is also important to note that based on the clinical findings thus far, DCS may not be effective under all circumstances (e.g. over prolonged treatment periods, in sub-clinical populations, when long intervals are between therapy sessions) [142]. Despite the high level of interest, to our knowledge, no study has yet been published on DCS efficacy in exposure therapy for PTSD although many are ongoing. There is also still much research needed to identify treatment and therapy strategies that optimize efficacy of behavioral therapy for PTSD [146].

The NMDA receptor antagonist ketamine has been proposed as a possible acute treatment for distress and depression in PTSD patients. This hypothesis is based on some efficacy in small trials of depression showing rapid depression reduction lasting up to 1 week post infusion [147, 148]. Like other non-competitive NMDA antagonists, ketamine interferes with memory consolidation [149], thus might be useful as an initial acute treatment for early PTSD. Currently there is at least one proof of principle clinical trial underway to test the utility of this drug class (Clinical trial identifier NCT00749203) in PTSD. However, others have questioned the risk/benefit of the competitive NMDA class as treatments due the side effect profile of drugs of this class including ketamine, which at higher doses includes neurotoxicity, psychosis and cognitive disruption [150]. Other NR2B receptor subunit antagonists are also under investigation, e.g. CP101,606, HON0001, with the hope of mitigating these potential side effects [For review

see Layton et al. [151]). Other possible glutamatergic cognitive enhancers that may benefit extinction therapy are positive allosteric modulators of AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) receptors [152]. However, such compounds require much more preclinical research and confirmation to support their use in humans.

5.2.2 Metabatropic glutamate receptor ligands—Overall, reductions in the glutamate signal have also been a potential targets for anxiolytic effects [153]. Such reductions can occur via activation of pre-synaptic regulatory receptors such as metabatropic glutamate 2/3 receptors (mGluR2/3) or blockade of post synaptic mGluR5 receptors [153]. The mGlu2/3 receptors are group II metabotropic receptors that when activated inhibit adenylate cyclase and suppress synaptic excitability via pre- and post-synaptic mechanisms [154]. These receptors are highly expressed in the cortex, amygdala and hippocampus, and thus are likely modulators of anxiety and fear responses.

In the late 90's the mGluR2/3 agonist LY35450 was shown to inhibit anxiety-like behavior in a number of rodent models [155] as well as to block the neuroendocrine response to stress [156]. In rodents and in non-anxious humans, acute LY345740 treatment has been shown to block expression of learned fear [155, 157]. mGlur2/3 agonists may reduce anxious responses via inhibition of basolateral amygdala output [158]. The potent blockade of learned fear behaviors and basolateral amygdala signaling suggests it may be useful for disorders like PTSD that involve contributions of cued fear responses to symptom provocation. Small proof of concept studies using a pro-drug of LY34570, LY544344, had shown promising results in GAD patients, however, pre-clinical findings of reduced seizure threshold have set back the development of these compounds [159].

Preclinical data over the last 10 years have shown clear evidence that mGluR5 antagonism or genetic deletion produces-anxiolytic-like effects on rodent behavior, both in unconditioned and conditioned stress models [160]. Fenobam is an inverse agonist for the mGluR5 receptor which has shown preliminary anxiolytic effects in early clinical trials, however it also produced some perceptual changes including hallucinations and vertigo, thus was dropped from further development [161]. Preclinical studies have indicated that mGluR5 antagonists may have psychotomimetic effects as they potentiate NMDA receptor antagonist induced disruptions in sensorimotor gating, and reduce social isolation [162]. However, a recent small non placebo controlled crossover study in Fragile X patients showed that fenobam treatment produced small but significant increases in sensorimotor gating, suggesting that underlying pathology may dictate the effects of fenobam on perceptual indices [163]. Although these results are intriguing, the adverse effect profile of mGluR5 agonists both pre-clinically and clinically suggest caution. Much more data are needed before testing in PTSD patient populations, which may be particularly sensitive to pro-psychosis side effects.

5.3.0 Monaminergic signaling

5.3.1 Reduction of Sympathetic arousal—Preclinical data have long suggested that noradrenergic activation strengthens emotional memory, thus leading to the hypothesis that noradrenergic blockade may help uncouple emotional memory from its strong physiological responses [164]. A number of agents are currently under investigation in clinical trials.

Propranolol: Initial un-blinded pilot studies supported the potential use of propranolol as a preventative treatment [165, 166]. However thus far, a larger double blind randomized placebo controlled study in post trauma surgical patients has not found propranolol to be effective as a preventative treatment for either depression or PTSD [167]. A recent small study showed efficacy to reduce physiological symptoms as adjunctive therapy in script driven trauma imagery [168], which is supported by its capacity in preclinical models to block fear memory

reconsolidation [169]. There are currently 9 listed clinical trials (clinicaltrials.gov). Three studies for propranolol use as a preventative or therapeutic treatment for PTSD are listed as completed as of Jan 2009, thus we will know much more about the utility of this compound soon.

Dopamine-beta hydroxylase is an enzyme involved in catecholamine synthesis that is critical to conversion of dopamine to norepinephrine. Plasma DBH has been shown to be lower in subjects with PTSD but not combat controls [170]. In a smaller study, PTSD subjects with psychosis were found to have higher plasma DBH than PTSD subjects without [171]. Thus it is not clear if DBH abnormalities contribute to PTSD. However, due to the possible increased responsiveness of PTSD subjects to noradrenergic activation [e.g. see Southwick et al. for review [172]], Nepicastat, a potent, selective, orally active inhibitor of dopamine-beta-hydroxylase is currently under study in a multisite trial for efficacy in treatment of chronic PTSD.

5.4 Neuropeptides

6.4.1 Neuropeptide Y (NPY)—Neuropeptide Y acts on a number of receptors, Y1, Y2, Y3, Y4 and Y5 that exert a number of physiological effects including anxiolysis, modulation of feeding and cardiovascular function. NPY signaling may be reduced in PTSD subjects [173]. In rodents, NPY appears to counteract anxiogenic effects of corticotropin releasing factor, which is observed to be excessively released in PTSD patients compared to controls [174]. In rats, central infusions of NPY have been shown to facilitate extinction, which may be via Y1 receptor activation since Y1 receptor antagonists are known to disrupt extinction [175]. Given the evidence supporting anxiolytic effects of Y1 receptor activation [176] these data give preliminary support for further research and development of a Y1 agonist for use in the treatment of PTSD symptoms as well as a prophylactic agent to foster resilience to trauma. One possible drawback to Y1 agonists as a chronic treatment however could be weight gain due to possible orexigenic side effects [177]. Although there are selective peptide Y1 agonists, no small molecule Y1 agonists have been reported to our knowledge.

5.4.2 CRF—PTSD patients have been shown to exhibit excess CRF CSF concentrations [174, 178, 179]. Exactly which specific symptoms of PTSD may be most reflected in these CRF alterations is unclear, however. None of these studies found a clear relationship between CRF levels and clinically rated PTSD symptoms. Although it is generally presumed that the observed CRF hypersecretion in PTSD patients occurs only after trauma, this assumption has yet to be tested. It is also possible that excess CRF release is a predisposing factor for PTSD, similar to findings of reduced hippocampal volume in twin studies of PTSD [180]. Indeed some pre-clinical studies (see below) indicate CRF receptor activation enhances fear learning, hence individuals with high CRF tone might develop stronger trauma related memories than those with lower CRF release.

Based on evidence for CRF dysfunction in depression and anxiety patients, CRF_1 and CRF_2 receptors, as well as the CRF binding protein, which may modulate ligand availability for receptor signaling, have all been proposed as pharmacotherapeutic targets for depression and anxiety disorders [181-183]. Potent, orally active small molecule CRF_1 antagonists have now been developed and are ready for human investigation [184]. Thus far clinical trials in depression have been disappointing. Although early, small clinical trials [185] were promising, more recent double blind placebo controlled studies for depression have been disappointing [186]. The side effect profile of these compounds is also a consideration; some compounds have been associated with liver damage. Given that CRF release is likely to be strongest immediately after trauma, and it is known to potentiate fear memory acquisition, it is possible that CRF_1 antagonists may be effective as a prophylactic treatment.

5.4.3 Oxytocin—The neuropeptide oxytocin is a nine amino acid peptide made in the hypothalamus and released into the blood from the posterior lobe of the pituitary gland. Oxytocin is synthesized in neurons in the hypothalamus that send processes to a variety of brain regions including the amygdala, which express some of the highest concentrations of oxytocin receptors in the nervous system [187]. In multiple clinical studies [188, 189]190 presentation of fear stimuli to normal patients, including aversive pictures such as emotional facial expressions, increased activity in the amygdala. This hyper-activation was blocked by nasal administration of oxytocin. Preclinical studies have shown that oxytocin may have anxiolytic effects as well as attenuate learned fear behaviors [191, 192]. A small study (n=15/group) in Vietnam veterans with PTSD showed some promise for intranasal oxytocin to reduce measures of arousal during exposure to personal trauma scripts [193]. Oxytocin is only 3 fold more potent at oxytocin versus vasopressin receptors, however, and prolonged stimulation of peripheral vasopressin receptors leads to antidiuresis, increasing the risk for hyponatremia and diminishing the therapeutic utility of this drug over time [194]. These studies suggest that development of highly selective oxytocin receptor agonists may produce therapeutic efficacy in treating PTSD and avoid the pronounced side effects of oxytocin itself. Oxytocin selective agonists are currently being developed by a number of companies.

5.5 Cannabinoids

The endogenous cannabinoid (CB) system, in particular the CB1 receptor, represents a potential therapeutic target for the treatment of a variety of learned fear-related disorders, including PTSD [195]. CB1 agonists have been shown to facilitate extinction while CB1 antagonism or gene deletion disrupts extinction [196]197198. However, there may be less of an effect if there is previous experience with CB1 agonism or under chronic treatment regimens [199]. Hence, like DCS, research on the most effective parameters and design regimens are necessary to better understand if these drugs show promise for facilitating extinction therapies.

6.0 Competitive Environment

Although there are few RCTs of compounds for PTSD, and yet fewer in which design and study execution allow for clear interpretation of results, nearly every class of potential compounds active in the central nervous system has been tried clinically and/or is represented in open label trials or case reports. Discussion of compounds in this manuscript is limited to those with published RCTs (Existing Treatment), or are compounds in active pre-clinical development or in early clinical trials (Scientific Rationale). Table 1 includes drugs currently marketed. Table 2 lists compounds under development.

7.0 Potential Development Issues

Currently available medications for treatment of PTSD provide limited benefit. The first line of treatment is antidepressants, usually SSRIs. Response is often incomplete; response rates hover around 60%, and less than 20-30% of patients fully remit [85, 200]. Despite the obvious need for more effective PTSD treatments, drug development has largely been focused on compounds for other indications, such as depression or other anxiety disorders. Clinical trials for PTSD are most often initiated after drugs are developed for these other indications, often years later, when the drug is nearing patent expiration. The lag in PTSD drug development may be due to the lack of reliable pre-clinical models, to slow acceptance of the PTSD diagnosis as a diagnostic entity, to a failure to recognize the prevalence of the disorder or to a perception that PTSD treatment trials are fraught with difficulty and that compounds studied are unlikely to show efficacy.

Indeed there may be issues specific to PTSD that proffer special challenges for PTSD research, some that are a characteristic of the population and others related to limited knowledge of the

disorder. First, the tendency of PTSD patients to avoid trauma reminders offers a special challenge in patient recruitment. PTSD subjects may be more likely to drop out than subjects with other diagnoses, at least until a solid clinical alliance is made. Secondly, the placebo rate, at about 25%, comparable to that of depression, is high, thus requiring relatively large cohorts to show statistical efficacy [6, 62]. And, deficits in our knowledge about subgroups, defined by demographics such as gender and ethnicity, or characteristics such as type and duration of trauma, longevity of symptoms or co-occurring psychiatric morbidities add to variability across studies, consequently impact the ability to interpret results and prove efficacy. Many of these impediments can only be remedied by research.

Other drug development issues, also common to other mental disorders are pharmacokinetic, in particular the transport of compounds to the CNS past the blood brain barrier. Transport systems include carrier- and receptor-mediated systems such as cationic and anionic influx and efflux systems (e.g., P-glycoproteins, multidrug resistance proteins, organic anion transporters) and others [201-204].

8.0 Expert Opinion

Despite epidemiological research showing PTSD to be a common mental disorder, development of pharmaceutical agents to treat PTSD symptoms has lagged that depression and other anxiety disorders, explained in part by its late inclusion in the DSM. Over the past few years, however, United States government funding for PTSD research, including for large scale clinical trials has expanded, a result of the recognition of increased rates of PTSD and suicidal behavior among troops returning from wars in Iraq and Afghanistan [205, 206]. As with other mental disorders, drug development for PTSD is hampered by an incomplete understanding of the natural history of the disorder, and by a lack of knowledge of the etiology and biological correlates of core PTSD symptoms and associated insomnia, depression and panic/anxiety that frequently fail to respond to current treatments.

Heightened interest and increased funding have provided for expanded PTSD research; large scale, multi-site clinical trials are underway on drugs to treat core PTSD symptoms (nepicastat), to treat targeted symptoms (prazosin) and as adjunct treatment in recalcitrant cases (risperidone). These trials should provide definitive answers on the efficacy of these compounds. In addition, there are a plethora of smaller scale trials of drugs with new mechanisms of action; these include trials with dual reuptake inhibitors, glucocorticoids, glucocortiocoid antagonists, and with stress system modulators, such as NPY. Moreover, there is a paradigm shift toward prophylaxis, i.e. attempted intervention with preventive and early intervention pharmacotherapies.

In order to achieve the goal of development of effective pharmacologic treatments for PTSD, improved knowledge of the natural history of PTSD and of etiological factors is crucial. Prospective, longitudinal studies that incorporate biological as well as psychosocial measures would help accomplish these goals. At present, there are least four such studies underway, three in military populations and one in police.

In addition, better pre-clinical models would be helpful. There may be fewer subtypes of PTSD, and less biological variability across the diagnosis than will ultimately be found in depression or schizophrenia. If so, this may bode well for drug development. And although there are as yet no universally agreed upon animal model for PTSD, there are a number in development based on fear learning that may be helpful in better understanding underlying biology and will prove to be effective models for translational drug testing.

In summary, current drugs used to treat PTSD or moderately effective at best. Much work is needed to develop effective treatment and prevention strategies.

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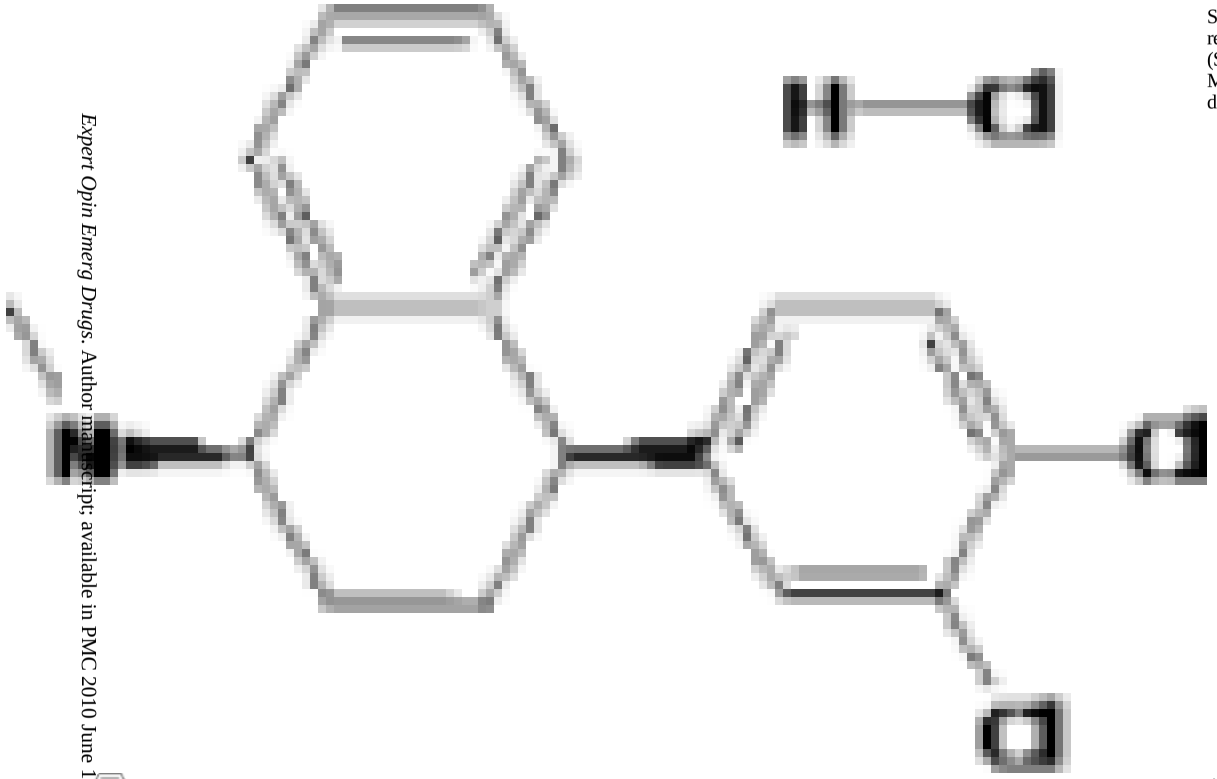
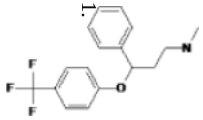
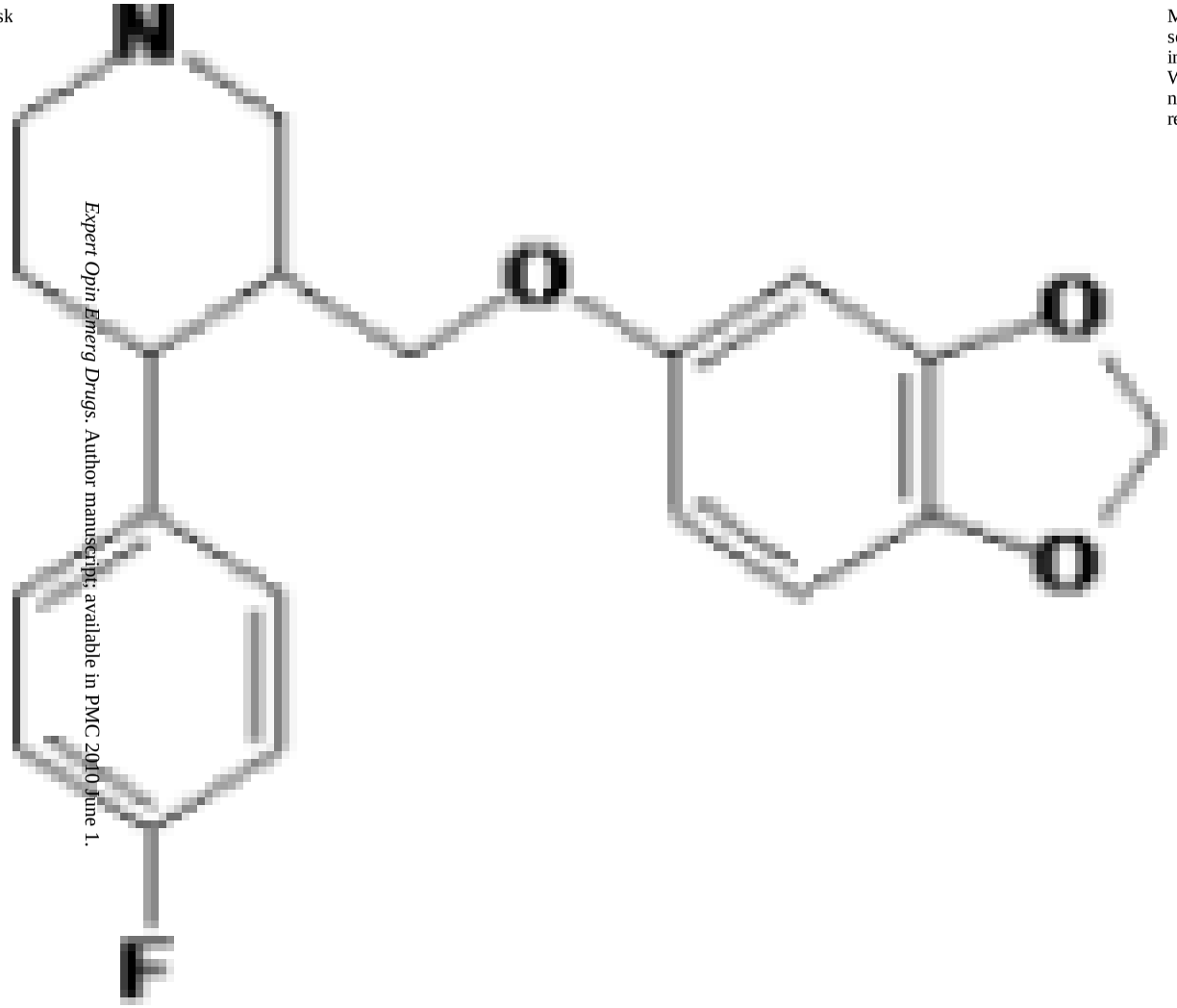
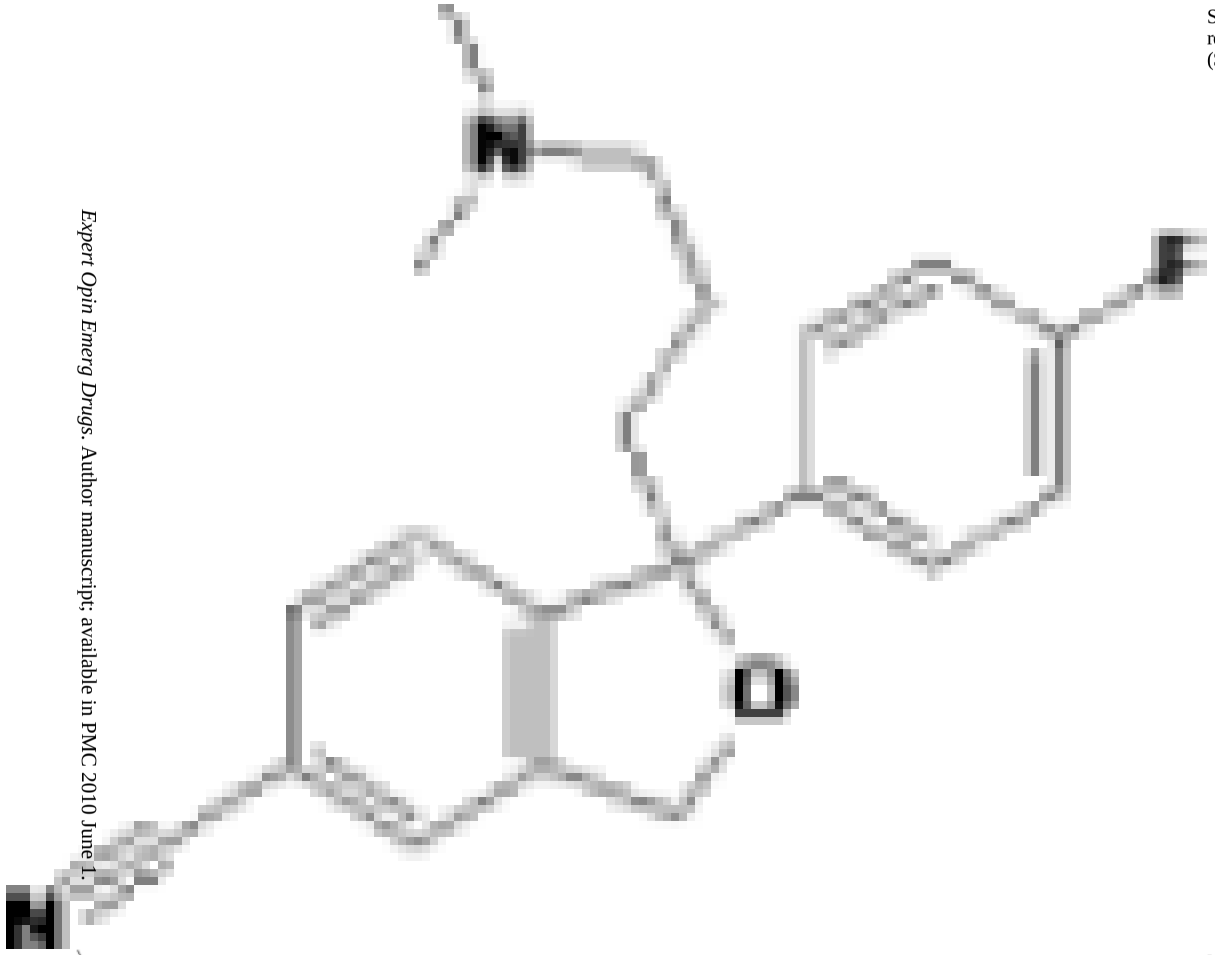
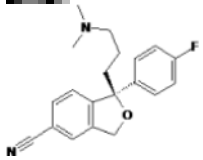
Table 1

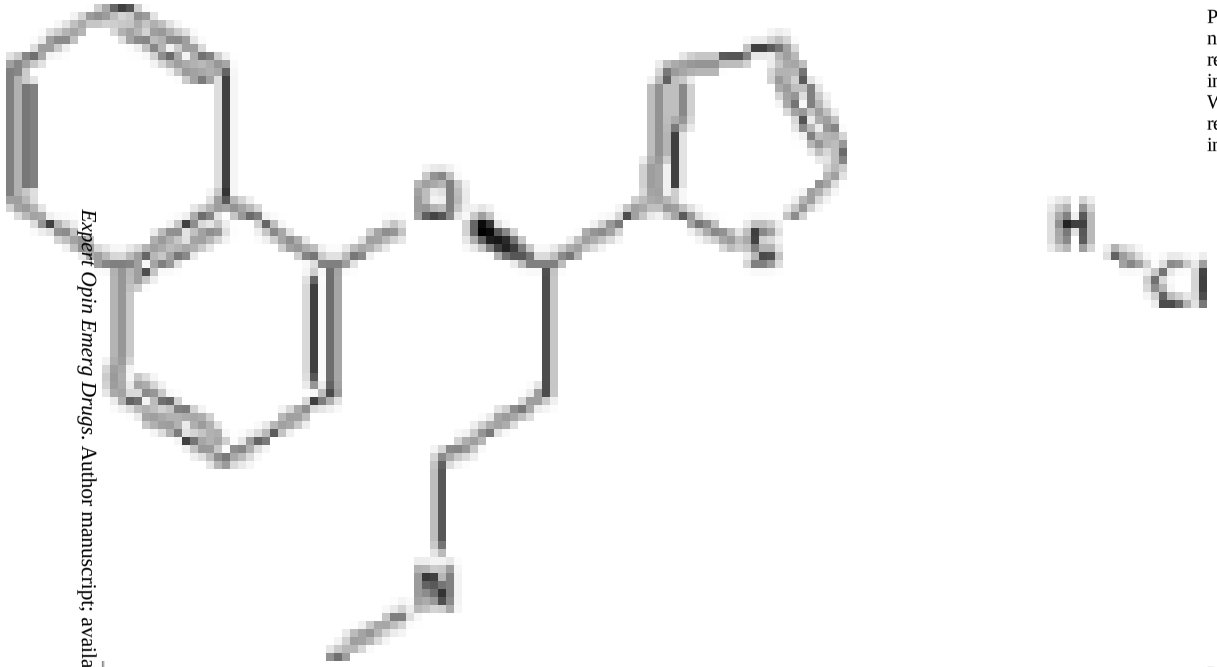
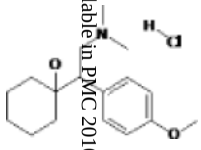
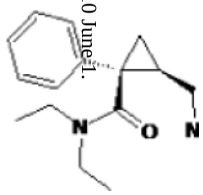
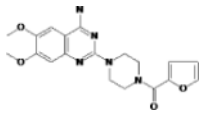
ugs with potential utility in PTSD

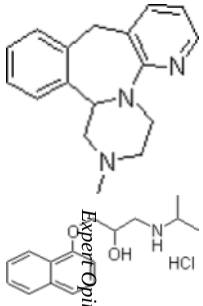
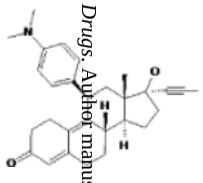
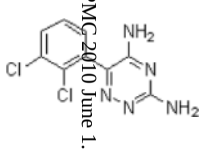
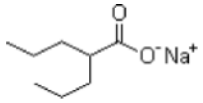
Company (originator)	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
Pfizer		Selective serotonin reuptake inhibitor (SSRI) Minor inhibitor of dopamine reuptake	Highest rate of nausea and diarrhea of SSRIs Headache Sexual side effects	Marketed	FDA approved for PTSD Only medication approved for long term treatment of PTSD	Posttraumatic stress disorder Major depression Social anxiety Panic Disorders Premenstrual syndrome Obsessive Compulsive Disorder
Eli Lilly & Co.		Atypical serotonin reuptake inhibitor (SSRI) Weak inhibition at the dopamine transporter	Nausea, Diarrhea, Headache, Sexual side effects Dopiminergic action may contribute to activation, akasthesia	Marketed	Commonly used in PTSD Long half-life and nonlinear kinetics FDA approved for children aged 8 and over	Major Depressive Panic Disorder Bulimia Premenstrual syndrome Obsessive-compulsive disorder

Company (originator)	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
Novo Nordisk		Most potent selective serotonin reuptake inhibitor (SSRI Weak inhibitor of norepinephrine reuptake	Nausea, Diarrhea Headache Sexual side effects Sexual side effects, Rare fatigue somnolence	Marketed	FDA approved for PTSD FDA warning may increase rate of birth defects taken in 1st trimester	Posttraumatic stress disorder Depressive and Anxiety Disorders Obsessive-compulsive disorder Premenstrual syndrome

Expert Opin Emerg Drugs. Author manuscript; available in PMC 2010 June 1.

Company (originator)	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
Lundbeck		Selective serotonin reuptake inhibitor (SSRI)	SSRI side effects may be fewer than with other SSRIs	Marketed	Used in PTSD Overdose concerns; seizures and QT interval prolongation	Major depression,
Forest Labs and Lundbeck		Newest and most selective SSRI Pharmacologically active S-isomer of citalopram	SSRI side effects may be fewer than with other SSRIs including citalopram	Marketed	Relatively fast onset of action Poster presentation ISTSS, 2005: Similar PTSD efficacy compared to sertraline	Major depression, general Generalized anxiety disorder Obsessive-compulsive disorder (registered)

Company (originator)	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
Eli Lilly & Co.		Potent serotonin and norepinephrine reuptake inhibitor Weak dopamine reuptake inhibitor	High rates of nausea during treatment initiation Insomnia Weight gain Increase in eye pressure	Marketed	Beneficial effects on physical pain PTSD clinical trial in progress	Major depression, Neuropathy, diabetic Generalized anxiety disorder Fibromyalgia (filed) Stress urinary incontinence (approved, Europe)
Wyeth Pharmaceu-ticals		Potent serotonin and norepinephrine reuptake inhibitor Weak dopamine reuptake inhibitor	Nausea Vomiting Can increase HR, BP and eye pressure	Marketed	Extended release formulation Significant treatment withdrawal symptoms	Major depression Generalized anxiety disorder Social anxiety Panic Disorder
Pierre Fabre Forest		Potent norepinephrine and serotonin reuptake inhibitor: 3/1 ratio	Nausea Vomiting Can increase HR, BP and eye pressure	Marketed	Beneficial effects on physical pain Antidepressant efficacy similar to SSRIs	Fibromyalgia Depression, bipolar (Phase II) Major depressive disorder (Phase II)
Pfizer		Selective alpha-1 adrenergic blocking agent	Orthostatic hypotension Syncope Headache Additive hypotensive effects	Marketed	Possible efficacy for nightmares and sleep in PTSD Large multi-site trial underway	Hypertension Heart failure

Company (originator)	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
		Alpha-2 adrenergic blocking agent Also blocks $5HT_2$ and $5HT_3$ receptors Potent antagonist at peripheral and central histamine receptors	Sedation at lower doses Weight gain Headache Additive hypotensive effects		Commonly used in PTSD Efficacy in PTSD not well studied	Major Depression
		Nonselective, beta-adrenergic blocking agent	Sedation at lower doses Lethargy Bradycardia Rare mental disturbance including hallucinations		Propranolol has been proposed as a PTSD prevention agent: studies are ongoing	Hypertension Angina Pectoris Other cardiac indications
Exelgyn		Glucocorticoid and progesterone receptor antagonist	Nausea Vomiting Abdominal pain	Marketed	There are ongoing clinical trials of glucocorticoid antagonists in depression; their use has been proposed in PTSD Their access to the CNS has not been determined	Medical abortion
Glaxo-Smith Kline		Inhibits voltage sensitive Na channels, thereby stabilizing membranes Modulation of pre-synpatic release of excitatory amino acids	Nausea Dizziness Double vision Headache	Marketed	Has mood stabilizing properties Rare adverse event: Stevens Johnson Syndrome Positive effect in one small (n=15) clinical trial in PTSD	Partial onset seizures Primary generalized tonic-clonic seizures mono- or adjunct therapy Lennox Gastaut Syndrome seizures Migraine prophylaxis
Abbott Laboratories		Blockade of voltage gated Na channels and T-type calcium channels Enhances GABA effects	Nausea Sedation Tremors Weight gain	Marketed	Has mood stabilizing properties May be useful in PTSD with co-morbid BAD	Partial onset seizures Primary generalized tonic-clonic seizures mono- or adjunct therapy Lennox Gastaut

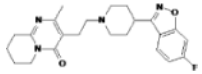
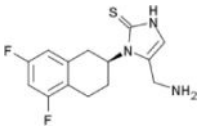
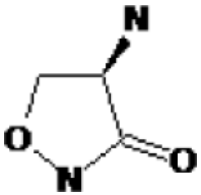
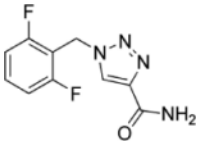
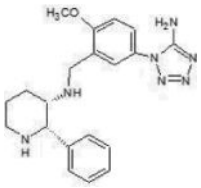
Company (originator)	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
		through GABA transaminase inhibition Also inhibits histone deacetylase			Contraindicated in pregnancy	Syndrome seizures Migraine prophylaxis
Johnson & Johnson		5-HT2$_A$ and dopamine D_2 antagonist	Somnolence Extra-pyramidal symptoms More rarely later state depressive symptoms	Marketed	Possible benefit as adjunctive treatment in chronic PTSD Large multi-site trial underway Metabolic effects (increased blood glucose, weight gain) common to atypical antipsychotics	Schizophrenia Acute mania Mixed manic episodes Autism, irritability

Table 2

Compounds in development for PTSD

Compound	Company	Structure	Mechanism of action	Side effects	Phase	Comments	Indication
Nepicastat	Synosia Therapeutics		Selective dopamine β-hydroxylase inhibitor	Nausea Diarrhea Dizziness Headache Full side effect profile to be established in multisite trial	Phase II Clinical Trials	Crosses the blood brain barrier Large multi-site trial underway	Post-traumatic stress disorder (Phase II) Addiction, cocaine (Phase II)
D-cycloserine	Searle (Monsanto; now Pfizer) Eli Lily & Co.		Partial NMDA (glycine) receptor agonist	Anxiety, disorientation, confusion in chronic dosing	Marketed	Possible benefit as adjunctive treatment in prolonged exposure treatment for PTSD Clinical trials underway	Previously used as an antibiotic against Mycobacterium tuberculosis
Rufinamide	Easai Synosia Therapeutics		Inhibits voltage sensitive Na channels, thereby stabilizing membranes	Somnolence Nausea Vomiting Headache Fatigue Dizziness	Marketed (Europe)	Has mood stabilizing properties Possible better adverse event profile than lamotrigine No report of Stevens Johnson to date	Lennox Gastaut Syndrome seizures Generalized Anxiety Disorder (Phase II)
NK1 antagonist GR 205171	Merck & Co		Neurokinin-1 inhibitor Substance P (SP) antagonist mediates effect via NK1 receptor	Not known	Marketed	Antidepressant anxiolytic and Antiemetic properties Cerebrospinal fluid SP is increased in PTSD NIH sponsored clinical trial in PTSD	Acute and delayed chemotherapy induced nausea and vomiting
CRF antagonist	Glaxo Smith Kline Neurocrine Biosciences, Johnson and Johnson, Pfizer, Bristol Meyers Squibb	Not available	Corticotropin-releasing hormone (CRF) R1 antagonist	Not known Hepatic side effects have limited previous CRF antagonist trials	Phase I and II Clinical Trials	Cerebrospinal fluid CRF is increased in PTSD	Major Depression Phase II Clinical Trial (Compound 561679) Anxiety-Depression Phase I Clinical Trial (Compound 586529)